REMARKS/ARGUMENTS

The September 25, 2003 Office Action has withdrawn a statutory double-patenting rejection, and § 102 rejection over Gould, et al. (U.S. Patent No. 5,587,402), Miller, et al. (Eiconsanoids and Other Bioactive Lipids in Cancer, Inflammation, and Radiation Injury 2:825-830, 1997), and Myers, et al. (WO 94/20080), and a § 103 rejection over Myers, et al. in view of Gould, et al., and Miller, et al. in view of Gould, et al.

The Examiner has proffered new grounds of rejection. Beginning on page 3 of the Office Action, the Examiner has rejected all pending claims under 35 U.S.C. § 103(a). In light of the arguments below, Applicants respectfully request reconsideration.

35 U.S.C. § 103(a) Rejection Over Haridas, et al.

The Office Action rejects claims 17, 18, 20 – 26 and 30 – 33 over Haridas, et al. The The Action describes Haridas, et al. as disclosing triterpene compositions and use thereof and notes that the "compositions comprise typically a monoterpene moiety or moieties . . . ." The Office Action goes on to describe "other components like 'immunomodulators'" and states that "the triterpene compositions may be administered to a subject to prevent cancer . . . ." The Office Action summarizes by observing that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to generate a method of sensitizing tumor/cancer cells to chemotherapy or immunomodulatory agents because Haridas, et al. disclose the use of monoterpene composition used in combination with chemotherapeutic agent or immodulatory agent . . . ."

Applicants dispute the Office Action's interpretation of Haridas, et al. Haridas, et al. does not disclose the use of "at least one monoterpene or sesquiterpene" as required by the claims at issue. Haridas, et al. describes the use of "monoterpene moiety or moieties." This

is a description of a very different molecule than that which is claimed. A standard chemistry textbook (Organic Chemistry: An Advanced Treatise, Henry Gilman, ed., 4:582, 1953) gives the following definition of terpenes, which is consistent with the conventional definition of "monoterpenes" and "sesquiterpenes" that Applicants mean to convey with their claim language:

> "The term terpenes originally designated a mixture of isomeric hydrocarbons of molecular formula $C_{10}H_{16}$ occurring in turpentine and many of the essential oils. At the present time the term refers to a large number of naturally occurring hydrocarbons of the formula (C_5H_8) and to an even larger number of substances from natural sources that may be looked upon as being derived from such hydrocarbons in various states of oxidation and unsaturation.
>
> The terpenes are usually classified according to the number of C_5H_8 units which they contain." (page 582)

Applicants note that the Gilman textbook goes on to characterize terpenes as divided into classes of molecular weight—monoterpenes have 10 carbon atoms; sesquiterpenes, 15; diterpenes, 20; and triterpenes, 30. Applicants have enclosed relevant pages from the textbook as Exhibit A.

Haridas, et al., describe the use of saponin mixtures containing a triterpene moiety to which monoterpenoid moieties are attached. These compounds under study are triterpenes and derivatized triterpenes. Referring to the definitions above and to the specification, triterpenes and monoterpenoid moieties do not belong to the class of monoterpenes or sesquiterpenes. Although Haridas, et al. attached a monoterpene moiety to the purified triterpene, they do not ascribe the biological endpoint of any of their findings to a particular monoterpene.

Rejection Under 35 U.S.C. § 103(a) Over Nakshatri, et al.

Claims 17, 18, 23 – 26 and 30 – 32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nakshatri, et al. Nakshatri, et al. describe the usefulness of parthenolide (a sesquiterpene lactone) as a chemo-sensitizer along with chemotherapeutic agents.

Similar to the argument proffered above, there are significant differences in both the structure and the of sesquiterpene lactones compared to monoterpenes and sesquiterpenes. Lactones are the cyclic esters of hydroxy acids, resulting from the internal elimination of water between the hydroxyl and carboxyl groups. This reaction takes place when the hydroxy acid is liberated from its salts by a mineral acid.

Applicants are not attempting to claim sesquiterpene lactones as part of the present invention.

Rejection Under 35 U.S.C. § 103 Over Haridas, et al. in view Gould, et al.

The Office Action has rejected claims 17 – 22 and 26 – 29 under 35 U.S.C. § 103(a) as being unpatentable over Haridas, et al. in view of Gould, et al. (U.S. Patent 5,587,402). Applicants have addressed Haridas, et al. above and remind the Examiner that Haridas, et al. does not disclose the use of a monoterpene or sesquiterpene.

Regarding U.S. Patent '402, the addition of the cytokine IL3 to cells treated with perillyl alcohol antagonizes the effect of perillyl alcohol on leukemic cells. The patent does not disclose a synergistic effect between cytokines and perillyl alcohol.

U.S. Patent '402 does not rectify the deficiencies of Haridas, et al. because U.S. Patent '402 does not disclose the use of monoterpene or sesquiterpenes with chemotherapy or immunumodulatory agents to sensitive tumor cells.

Rejection Under 35 U.S.C. § 103(a) Over Haridas in view of Myers, et al.

The Office Action has rejected claims 17, 18, 20, 21, 26, 28 and 29 under 35 U.S.C. § 103(a) as being unpatentable over Haridas, et al. in view of Myers, et al. (WO 94/20080). Applicants have discussed Haridas, et al. and note that Haridas does not disclose the use of monoterpenes or sesquiterpenes.

Myers, et al. does disclose the use of monoterpenes and sesquiterpenes in the treatment of cancer. The Office Action notes that "in addition a method of sensitizing a cancer to radiation is disclosed that involves administering an effective amount of the terpene to a mammal."

Applicants note that the pending claims are no longer drawn to radiation methods but are drawn only to the combination of chemotherapy and monoterpenes/sesquiterpenes and immunomodulatory agents and monoterpenes/sesquiterpenes. Myers, et al. is irrelevant to these methods and does not rectify the deficiencies of the Haridas reference.

Applicants believe claims 17 – 33 to be allowable and request speedy allowance. Applicants believe no fees to be necessary to enter these remarks. However, if fees are necessary, please charge Deposit Account 17-0055.

Respectfully submitted,

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CHAPTER 7

THE TERPENES

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CONTENTS

INTRODUCTION

The term *terpenes* originally designated a mixture of isomeric hydrocarbons of molecular formula $C_{10}H_{16}$ occurring in turpentine and many of the essential oils. At the present time the term refers to a large number of naturally occurring hydrocarbons of the formula $(C_5H_8)_n$ and to an even larger number of substances from natural sources that may be looked upon as being derived from such hydrocarbons in various states of oxidation and unsaturation.

The terpenes are usually classified according to the number of C_5H_8 units which they contain.

$C_{10}H_{16}$	Monoterpenes	$C_{30}H_{48}$	Triterpenes
$C_{15}H_{24}$	Sesquiterpenes	$C_{40}H_{64}$	Tetraterpenes
$C_{20}H_{32}$	Diterpenes	$(C_5H_8)_x$	Polyterpenes

The terpenes thus range from relatively simple hydrocarbons, $C_{10}H_{16}$, through large molecules such as lutein, $C_{40}H_{56}O_2$, to polymers of high molecular weight such as rubber, $(C_5H_8)_x$. As a class the terpenes rank with the alkaloids and the carbohydrates in the chemical interest which they have stimulated and in their practical uses.

The most important structural feature which the terpenes have in common is their relation to the carbon skeleton of isoprene, $CH_2{=}C(CH_3){-}CH{=}CH_2$. The great majority of terpenes may be looked upon as derived from the carbon skeletons of dimers, trimers, tetramers, etc., of isoprene. The even divisibility of the carbon skeletons of terpenes into *iso*-C_5 units is known as the *isoprene rule*[1] and has been of

[1] Wallach, *Ann.*, **238**, 78 (1887); **239**, 49 (1887).

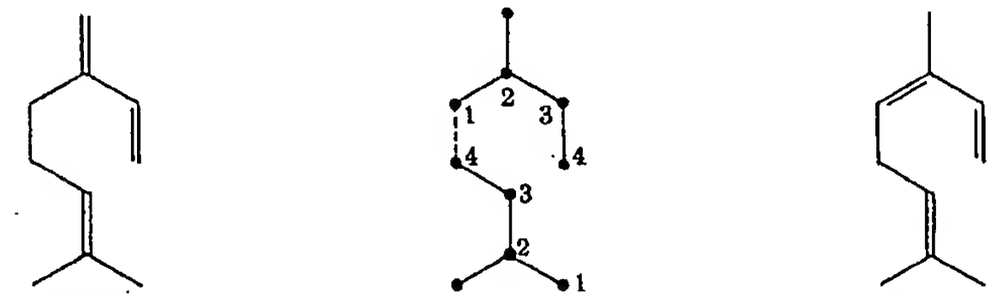
tremendous value as a working hypothesis in the determination of structure.[2]

TERPENES

The molecular formula for the monoterpenes, $C_{10}H_{16}$, represents a deficiency of six hydrogen atoms relative to the corresponding saturated hydrocarbon, $C_{10}H_{22}$. The missing hydrogen atoms can be accounted for in the following ways: (1) acyclic monoterpenes with three double bonds; (2) cyclic monoterpenes with two double bonds; (3) bicyclic monoterpenes with one double bond; (4) tricyclic monoterpenes with no double bond. Compounds of all four types are known.

Acyclic Terpenes

Hydrocarbons. Few of this class are known, although substances which may be looked upon as their oxygen derivatives are plentiful. The most important hydrocarbons are *myrcene* and *ocimene*, which occur in the essential oils of bay and *Ocimum basilicum*, respectively.



Myrcene I Ocimene

The carbon skeletons of myrcene and ocimene provide the simplest example of the isoprene rule. Here the number 1 carbon atom of one *iso*-C_5 unit is joined to the number 4 carbon atom of the second unit. This arrangement (I) is the more usual in terpenes and is known as the *head-to-tail* arrangement.

Myrcene is an oil, b.p. 166–168°. The ultraviolet absorption spectrum shows an intense maximum at 224 mμ indicative of a conjugated system of double bonds.[3] Reduction with sodium in alcohol produces a dihydromyrcene, further proving that a conjugated system is present.[4] Ozonolysis followed by chromic acid and hypobromite oxidation of the crude ozonolysis product gives only succinic acid.[5] These observations re-

[2] For a possible exception to the rule see Gillam, Lynas-Gay, Penfold, and Simonsen, *J. Chem. Soc.*, 60 (1941).

[3] Booker, Evans, and Gillam, *ibid.*, 1453 (1940).

[4] Semmler, *Ber.*, **34**, 3126 (1901).

[5] Ruzicka and Stoll, *Helv. Chim. Acta*, **7**, 272 (1924).